ADVANCES IN OBESITY PHARMACOTHERAPY

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DISCLOSURE STATEMENT

Dr. Wyatt has served as an advisor for Wellspring Camps, Retrofit Inc. and Eisai Inc.
She receives royalties from Up to Date and has received grant funding from the NIH, Orexigen, Novo Nordisk and GI Dynamics.
She regularly speaks for CME Incite on obesity treatment.
She has ownership interests in Active Planet LLC and has co-ownership on a patent for a weight loss maintenance strategy – The Energy Gap.

LEARNING OBJECTIVES

After taking part in this activity, participants will be able to:

• Identify FDA approved weight loss medications
• Discuss the risks and benefits of prescribing weight loss medications in their overweight and obese patients
• Describe strategies for prescribing weight loss medications
HISTORY OF THE “NEGATIVE HALO” FOR WEIGHT LOSS MEDICATIONS

- Negative halo of addictive properties of amphetamine
- Tarnished past history
- Perception drugs are ineffective because patients regain weight when drugs are stopped
- Misbelief obesity is simply a result of poor willpower—(i.e., obese people do not really need or deserve a drug)
- Do real doctors treat obesity?

GAME PLAN

- Who can use a Weight Loss Medication?
- What Drugs are Available?
- How are they Prescribed?
- Are they Safe? Are they Effective?

IN 2013 THE MOST EXCITING ADVANCES IN OBESITY TREATMENT ARE IN DRUG THERAPY
WHO IS A CANDIDATE FOR A WEIGHT LOSS MEDICATION?

- Treatment is commensurate with risk
- Balance benefit of weight loss to risk of medication
- The more benefit from a weight loss the more risk you might take in a treatment
- The more risk from not losing weight the more risk in a treatment

CURRENT APPROACH TO OBESITY TREATMENT

<table>
<thead>
<tr>
<th>TREATMENT OPTIONS</th>
<th>Current Patient Risk LOW</th>
<th>Current Patient Risk HIGH</th>
<th>Patient Risk LOW</th>
<th>Patient Risk HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI Range</td>
<td>25-29.9</td>
<td>30-34.9</td>
<td>35-39.9</td>
<td>≥40</td>
</tr>
<tr>
<td>Diet, Exercise and Behavioral Therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
<td></td>
<td>with a comorbidity</td>
<td>+</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>with a comorbidity</td>
<td>+</td>
</tr>
</tbody>
</table>

Wyatt HR. JCEM April 2013
Lorcaserin

- Selective serotonin 2C receptor agonist that works by decreasing food intake.
- Mechanism of action is similar to fenfluramine and dexfenfluramine except it is specific for the 2C serotonin receptor that is not found on the heart or heart valves.
- The result is increased satiety effect and no heart valve damage. Echo studies showed no increased incidence of FDA-defined cardiac valvulopathy. There is some concern the studies were not powered adequately for complete confidence because of a lower than expected event rate.
- The FDA advisory panel voted in favor of approval 18-4 in May 2012 and lorcaserin was officially approved by the FDA in June 2012.
- It should be available in 2013.
WEIGHT CHANGE OVER 104 WEEKS WITH LORCASERIN THERAPY - BLOOM


CATEGORICAL WEIGHT CHANGE OVER WITH LORCASERIN THERAPY - BLOOM


WEIGHT CHANGE OVER 52 WEEKS WITH LORCASERIN THERAPY - BLOOM-DM

EFFECT OF LORCASERIN ON GLYCEMIC PARAMETERS- BLOOM-DM

All Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo, n=248</th>
<th>Lorcaserin 10 mg BID, n=251</th>
<th>P Value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>160.0 ± 41.6</td>
<td>163.6 ± 48.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-11.9 ± 2.5</td>
<td>-27.4 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0 ± 0.9</td>
<td>8.1 ± 0.9</td>
<td>0.125</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.4 ± 0.6</td>
<td>-2.3 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin (µU/mL)</td>
<td>16.2 ± 14.7</td>
<td>15.0 ± 10.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-1.6 ± 0.7</td>
<td>-2.3 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*LS mean change from baseline for lorcaserin 10 mg BID compared to control for continuous variables; Fisher's exact test for categorical variables.


EFFECT OF LORCASERIN IN METABOLIC MEASURES

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo, n=248</th>
<th>Lorcaserin 10 mg BID, n=251</th>
<th>P Value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>35.8 ± 4.5</td>
<td>36.1 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.6 ± 0.1</td>
<td>-1.6 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>126.5 ± 13.5</td>
<td>126.6 ± 12.7</td>
<td>0.891</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.9 ± 0.9</td>
<td>-0.8 ± 0.8</td>
<td>0.891</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78.7 ± 7.9</td>
<td>77.9 ± 8.0</td>
<td>0.563</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.7 ± 0.6</td>
<td>-1.1 ± 0.6</td>
<td>0.563</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>172.0 ± 35.7</td>
<td>173.5 ± 35.3</td>
<td>0.714</td>
</tr>
<tr>
<td>% Change</td>
<td>-0.1 ± 1.2</td>
<td>-0.7 ± 1.1</td>
<td>0.714</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>94.6 ± 30.2</td>
<td>95.0 ± 30.4</td>
<td>0.802</td>
</tr>
<tr>
<td>% Change</td>
<td>-5.0 ± 2.6</td>
<td>-4.2 ± 2.6</td>
<td>0.802</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>45.7 ± 12.7</td>
<td>45.3 ± 11.0</td>
<td>0.005</td>
</tr>
<tr>
<td>% Change</td>
<td>1.6 ± 1.0</td>
<td>5.2 ± 1.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>163.5 ± 87.5</td>
<td>172.1 ± 103.6</td>
<td>0.054</td>
</tr>
<tr>
<td>% Change</td>
<td>-4.8 ± 2.5</td>
<td>-10.7 ± 2.4</td>
<td>0.054</td>
</tr>
</tbody>
</table>

*LS mean change from baseline for lorcaserin 10 mg BID compared to control.

Data are presented from MITT/LOCF population as follows: baseline value ± SD; change from baseline least squares mean ± SEM.

LORCASERIN SAFETY DATA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo, n=248</th>
<th>Lorcaserin 10 mg BID, n=251</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>37 (14.5)</td>
<td>30 (11.7)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>29 (11.3)</td>
<td>22 (8.4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (9.4)</td>
<td>8 (3.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>23 (9.0)</td>
<td>9 (3.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Cough</td>
<td>21 (8.2)</td>
<td>5 (2.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Symptomatic hypoglycemia</td>
<td>19 (7.4)</td>
<td>10 (4.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (7.4)</td>
<td>5 (2.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gastroenteritis, viral</td>
<td>18 (7.0)</td>
<td>5 (2.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (7.0)</td>
<td>11 (4.4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Influenza</td>
<td>15 (5.9)</td>
<td>8 (3.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>13 (5.1)</td>
<td>0 (0.0)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

*LS mean change from baseline for lorcaserin 10 mg BID compared to control.

Data are presented from MITT/LOCF population as follows: N (% of patients).

HOW I SEE THE FUTURE ROLE OF LOCASERIN

• While locaserin meets FDA weight loss criteria, the efficacy is modest, but the risk profile is also low.
• For this drug, it is important for clinicians to realize that certain individuals may respond more (have a significantly greater weight loss) than other individuals.
• This drug may be one that eventually will be helpful in a smaller subset of obese “responders”
• Locaserin’s reduction in HbA1c levels appears more substantial than the weight loss reduction in the BLOOM-DM study and therefore diabetics may also prove to be a subset that may have greater benefit
• Locaserin has not been studied in combination with other drugs such as phentermine. While combining the two drugs (phentermine and locaserin) may increase weight loss, the safety of the combination has not been evaluated

PHENTERMINE AND TOPIRAMATE (PHEN/TPM)

• Phentermine induces central NE release and promotes weight loss by decreasing food intake. It is currently approved as a monotherapy for only short-term use.
• Topiramate monotherapy (200-400 mg/day) was approved in 1996 for the treatment of seizures and in 2004 for migraine prophylaxis (100mg/ day) and is currently not approved as a monotherapy for weight management.
• Topiramate exhibits a combination of properties such as effects on sodium channels, enhancements of GABA-activated chloride channels, and inhibition of carbonic anhydrase isoenzymes, but the specific mechanism promoting weight loss is unclear.
• In combination the drugs have shown greater weight reduction than either agent alone.

PHENTERMINE AND TOPIRAMATE (PHEN/TPM)

• Higher dose topiramate trials as a monotherapy were halted because of the cognitive and depressive side effects.
• The combination of PHEN/TPM allows a lower dose of controlled release topiramate to be used and therefore a more acceptable adverse events profile.
• The drug combination of phentermine and topiramate received a 20-2 in favor vote from the February 2012 FDA advisory panel and was FDA approved in July of 2012. It became available for use in late 2012.
STUDY DESIGN: 56-WEEK STUDY FOLLOWED BY 52-WEEK EXTENSION- CONQUER AND SEQUEL


Conducted between December 2008 and June 2010.

All subjects participated in a lifestyle modification program

<table>
<thead>
<tr>
<th>Treatment (56 weeks)</th>
<th>Treatment (52 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>n=984</td>
<td>n=227</td>
</tr>
<tr>
<td>7.5 mg phentermine/46 mg topiramate (PHEN/TPM ER 7.5/46) n=498</td>
<td></td>
</tr>
<tr>
<td>15 mg phentermine/52 mg topiramate (PHEN/TPM ER 15/52) n=993</td>
<td></td>
</tr>
</tbody>
</table>

All subjects participated in a lifestyle modification program

EFFECT OF PHENTERMINE/TOPIRAMATE ER ON WEIGHT LOSS IN OBESE ADULTS AFTER 1 YEAR- CONQUER


*P<0.001 vs placebo

EFFECT OF PHENTERMINE/TOPIRAMATE ER ON WEIGHT LOSS IN OBESE ADULTS AFTER 1 YEAR- CONQUER

EFFECT OF PHENTERMINE/TOPIRAMATE ON BLOOD PRESSURE AND LIPID LEVELS IN OBESE ADULTS AFTER 1 YEAR

EFFECT OF PHENTERMINE/TOPIRAMATE ER ON GLUCOSE LEVELS IN OBESE ADULTS WITH TYPE 2 DIABETES AFTER 1 YEAR

EFFECT OF PHENTERMINE/TOPIRAMATE ER ON WEIGHT LOSS IN OBESE ADULTS OVER 2 YEARS
PHENTERMINE/TOPIRAMATE ER SAFETY DATA

<table>
<thead>
<tr>
<th>Section</th>
<th>Event</th>
<th>Placebo</th>
<th>PHEN/TPM ER 7.5/46</th>
<th>PHEN/TPM ER 15/92</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>13</td>
<td>12.8481</td>
<td>12</td>
<td>12.8481</td>
<td>&lt;0.0001</td>
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<tr>
<td>Paraesthesia</td>
<td>2</td>
<td>14</td>
<td>12.8481</td>
<td>12</td>
<td>12.8481</td>
<td>&lt;0.0001</td>
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<tr>
<td>Constipation</td>
<td>6</td>
<td>15</td>
<td>12.8481</td>
<td>12</td>
<td>12.8481</td>
<td>&lt;0.0001</td>
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<tr>
<td>URI</td>
<td>13</td>
<td>12</td>
<td>0.7422</td>
<td>12</td>
<td>0.7422</td>
<td>0.7422</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9</td>
<td>11</td>
<td>0.2204</td>
<td>12</td>
<td>0.2204</td>
<td>0.2204</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1</td>
<td>7</td>
<td>&lt;0.0001</td>
<td>12</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Insomnia</td>
<td>5</td>
<td>6</td>
<td>0.3832</td>
<td>12</td>
<td>0.3832</td>
<td>0.3832</td>
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<tr>
<td>Headache</td>
<td>9</td>
<td>7</td>
<td>0.1983</td>
<td>12</td>
<td>0.1983</td>
<td>0.1983</td>
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<tr>
<td>Dizziness</td>
<td>3</td>
<td>7</td>
<td>0.0005</td>
<td>12</td>
<td>0.0005</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7</td>
<td>7</td>
<td>1.0000</td>
<td>12</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
<tr>
<td>Back pain</td>
<td>5</td>
<td>6</td>
<td>0.6199</td>
<td>12</td>
<td>0.6199</td>
<td>0.6199</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>4</td>
<td>0.6754</td>
<td>12</td>
<td>0.6754</td>
<td>0.6754</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>4</td>
<td>0.7010</td>
<td>12</td>
<td>0.7010</td>
<td>0.7010</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5</td>
<td>6</td>
<td>0.2229</td>
<td>12</td>
<td>0.2229</td>
<td>0.2229</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>4</td>
<td>4</td>
<td>0.7729</td>
<td>12</td>
<td>0.7729</td>
<td>0.7729</td>
</tr>
<tr>
<td>UTI</td>
<td>4</td>
<td>5</td>
<td>0.1753</td>
<td>12</td>
<td>0.1753</td>
<td>0.1753</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>5</td>
<td>0.5373</td>
<td>12</td>
<td>0.5373</td>
<td>0.5373</td>
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<tr>
<td>Bronchitis</td>
<td>4</td>
<td>4</td>
<td>1.0000</td>
<td>12</td>
<td>1.0000</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

REMS TRAINING FOR PHEN/TPM ER

- PHEN/TPM ER is contraindicated during pregnancy
- PHEN/TPM ER has been approved with a REMS training program to inform clinicians and patients about
  - Increased risk of congenital malformation, specifically orofacial clefts, in infants exposed to PHEN/TPM ER during the first trimester of pregnancy
  - Importance of pregnancy prevention for females of reproductive potential receiving PHEN/TPM ER
  - Need to discontinu PHEN/TPM ER immediately if pregnancy occur

http://www.qsymiarems.com/

HOW TO PRESCRIBE INFO

- PHEN-TPM ER is available only by mail order from the certified pharmacies
- Certified pharmacies include CVS, Express Scripts, Walgreens, and Walmart.
- Two separate prescriptions need to be submitted for PHEN-TPM ER: the first for 14 days on a starting dose of 3.75 mg/23 mg and the second for 30 days on the recommended dose of 7.5 mg/46 mg. Take once daily in the morning.
- Once the prescriptions and accompanying Universal Form are received, the pharmacy will contact the patient for payment, and the drug will be delivered to the patient's home.
PHYSICIAN DIRECTED WEIGHT LOSS CLINIC
SPECIALIZING IN EVALUATION AND INCORPORATION OF
WEIGHT LOSS MEDICATIONS FOR OBESITY TX

- Weight Loss Specialists with expertise and experience in using obesity medications
- Evaluate if patient is appropriate, evaluate risk-benefit
- Prescribe and monitor efficacy and side effects of medications
- Add adjunctive diet and activity plan
- FDA approved meds and some Off label use
- Phentermine/topiramate, phentermine, locaserin (when available), bupropion/naltrexone, and bupropion/zonisamide

HOW I SEE THE FUTURE ROLE OF PHEN/TPM

- Weight loss with the combination of PHEN/TPM is better than any of the obesity drugs in the pipeline at this time.
- Along with this increase in efficacy however comes a more troublesome risk profile that clinicians need to understand and actively address with their patients.
- Depression and cognitive issues have not been major issues in the more recent controlled release trials.
- Cardiovascular events and birth defects appear to be the issues that will need to be monitored closely.

EMERGING PHARMACOTHERAPY

| Agent | Naltrexone/BupSR | Liraglutide
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Status</td>
<td>FDA requested additional/Phase 3 trials</td>
<td>In Phase 3 clinical trials</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Naltrexone, opioid receptor antagonist; Bup, norepinephrine-dopamine reuptake inhibitor</td>
<td>Glucagonlike peptide-1 analogue</td>
</tr>
<tr>
<td>Follow-up Duration</td>
<td>56 weeks</td>
<td>56 weeks</td>
</tr>
<tr>
<td>Common AEs</td>
<td>Nausea, Headache, Constipation, Dizziness, Vomiting, Dry mouth</td>
<td>Nausea, Vomiting, Gastro-intestinal effects</td>
</tr>
</tbody>
</table>

**NALTREXONE AND BUPROPION (NAL/BUP)**

- The Naltrexone SR/Bupropion SR combination functions as an opioid receptor antagonist combined with a norepinephrine and dopamine receptor reuptake inhibitor.
- Bupropion has neuronal effects that lead to reduced energy intake and increased energy expenditure.
- Naltrexone was chosen as a complement to bupropion in order to block compensating mechanisms that attempt to prevent long-term, sustained weight loss.
- The FDA advisory panel voted in favor of approval (13-7) of this combination in December of 2010 however the FDA declined to approve the drug in early 2011 going against the advisory panel recommendation.

**NALTREXONE AND BUPROPION (NAL/BUP)**

- The FDA is requiring large scale safety study evaluating cardiovascular events. This was an interesting decision by the FDA given buproprion which is the drug potentially associated with the increase in cardiovascular risks, is currently available and used by millions of Americans for the treatment of mild depression or to stop smoking.
- Blood pressure and pulse were slightly increased indicating the potential for an increased cardiovascular events. Increased risk of seizures as well as syncope in the treatment group was also a safety concern that was noted.
- A study of this size and scope will take tremendous resources and time to complete. The earliest this drug could be approved is late 2014 or early 2015.

**WEIGHT LOSS WITH NALTREXONE SR/BUPROPION SR COMBINATION THERAPY AS AN ADJUNCT TO BEHAVIOR MODIFICATION: THE COR-BMOD TRIAL**

Wadden et al. (2011) Obesity 19, 110–120.
ALGORITHM FOR PRESCRIBING WEIGHT LOSS MEDICATION

- Establish if an appropriate candidate
- Establish if the patient is motivated to lose weight
- Set a weight loss goal
- What nonRX treatment options do you implement?
- Add medication- when, what and how for best outcomes?

ADVANCES IN OBESITY TREATMENT
WEIGHT MANAGEMENT PARADIGM EVOLUTION

Acute Weight Loss
- Strategy

Chronic Weight Loss
- Strategy

Weight Loss
- Strategy 1
- Strategy 2

4-6 months
- Years/Forever?

POSSIBLE METHODS OF SEQUENCING BEHAVIORAL AND PHARMACOLOGICAL THERAPIES FOR IMPROVEMENT IN OUTCOMES

- Concurrent Administration
- Lifestyle followed by Pharmacotherapy
- Medication for Weight Loss Maintenance
- Intermittent Use of Medications

EFFECT OF CONTINUOUS AND INTERMITTENT PHENERMINE THERAPY ON BODY WEIGHT

![Graph showing weight loss over time for continuous and intermittent phentermine therapy.](image)


DM TREATMENT 20 YEARS AGO

- Only a few drugs
- Glucose control was not as tight
- Combination medications, and multiple types of medications have allowed better control
- Subgroups of people
- Obesity pharmacotherapy is in its infancy

WHY I PRESCRIBE WEIGHT LOSS MEDICATIONS

- Obesity is a chronic disease
- Treat it like other chronic diseases
- Small weight loss has legitimate health benefits
- It's behaviorally and physiologically hard to maintain a weight loss
- Side effects are in the eyes of the person experiencing them
- We prescribe medications that cause weight gain all the time
- They are not going away
- She is asking you for evidence based weight management strategies- if not you who should she get the information/medication from?